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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/776,350	04/18/1997	ALASDAIR R. MACLEAN	117-231	1818

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EXAMINER
UNGAR, SUSAN NMN

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 05/10/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	08/776,350	Applicant(s)
Examiner	Susan Ungar	Art Unit 1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM
THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) Responsive to communication(s) filed on 17 February 2004.
2a) This action is FINAL. 2b) This action is non-final.
3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4) Claim(s) 43-45, 47, 51 and 59 is/are pending in the application.
4a) Of the above claim(s) _____ is/are withdrawn from consideration.
5) Claim(s) _____ is/are allowed.
6) Claim(s) 43-45, 47, 51 and 59 is/are rejected.
7) Claim(s) _____ is/are objected to.
8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9) The specification is objected to by the Examiner.
10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) All b) Some * c) None of:
1. Certified copies of the priority documents have been received.
2. Certified copies of the priority documents have been received in Application No. _____.
3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) Notice of References Cited (PTO-892)
2) Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date 2/17/04.

4) Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
5) Notice of Informal Patent Application (PTO-152)
6) Other: _____.

1. The Amendment filed February 17, 2004 in response to the Office Action of October 14, 2003 is acknowledged and has been entered. Previously pending claims 1-42, 46, 48-50, 52-58 have been cancelled and claims 43, 45, 47, 59 have been amended. Although the amendment cancels claims 42-58, in the interests of compact prosecution, since the amendment amended claims 43, 45, 47 and cancelled claims 46 and 48-50, it is will be assumed for examination purposes that the cancellation of claims 42-58 after the presentation of claim 51 was an unintentional typographical error and that cancellation of claims 52-58 were intended by Applicant. Confirmation of the cancellation as a typographical error and appropriate correction is required. Claims 43-35, 47, 51, 59 are currently being examined.
2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

New Grounds of Rejection

Claim Rejections - 35 USC 103

3. Claims 43-45, 47, 51, 59 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6,139,834 in view of WO 92/13943, IDS item and Amer et al (Cancer, 1978, 42:660-668) or Budman et al (Eur. J. Cancer, 1978, 14:327-330), and MacLean et al (J. Gen. Virol., 1991, 72:631-639) and Bolovan et al (J. Virology, 1994, 68:48-55) and Olafsson et al (Arch. Virol., 1993, 128:241-256, of record).

The claims are drawn to a method of treating a metastatic tumor which occurs in but does not originate from the central nervous system of a human comprising intratumoral or intracranial injection of an avirulent HSV-1 consisting of an HSV-1 genome wherein such modification consists of a mutation in the

gamma 34.5 gene so as to become a non-functional gamma 34.5 gene, wherein the avirulent HSV1 infects and replicates within the tumor cells of tumor, wherein the metastatic tumor occurs in brain, wherein the metastatic tumor is metastasized melanoma, wherein the modified virus is modified by deletion within the BamHI s restriction fragment of the RL terminal repeat wherein the mutant is strain 1716.

U.S. Patent No. 6,139,834 teaches the use of a replication-competent viral vector, preferably a HSV suitable for use in humans, that is capable of killing human tumor cells *in vivo* that exhibit hypersensitivity to anti-viral agents and an inability to revert to wild-type virus and that is not neurovirulent at a dose required to kill tumor cells (see col. 3, lines 10-17: col. 4, lines 14-22). U.S. Patent No. 6,139,834 also teaches that viruses have been tested in the prior art for their ability to treat various types of tumors in animals and humans via direct cell killing by the virus, called oncolysis, and that for use as antineoplastic agents these viruses have been genetically altered so that they are not capable of replication in non-dividing cells to avoid systemic infection (see col. 1, line 44 continues to line 5 of col. 2). In a preferred embodiment, U.S. Patent No. 6,139,834 teaches the delivery of a pharmaceutical composition comprising (A) a herpes simplex virus vector that is altered in (i) the y34.5 gene, and (ii) the ribonucleotide reductase gene; and (B) a pharmaceutically acceptable vehicle for said vector, such that said tumor cells are altered *in situ* by said vector, whereby said tumor cells are killed, the same method wherein said tumor cells are selected from a group including melanoma cells (See the entire patent and particularly claims 1 and 3). An exemplary mutant herpes simplex virus, G207, disclosed by U.S. Patent No. 6,139,834 contains a 1-kB deletion in both copies of the y34.5 gene within the BamHI fragment of the long terminal repeat of the viral genome (See Figures 1, 2 and column 15, lines 36-45).

The mutant herpes simplex virus can be derived from either HSV-I or HSV-2 (column 4, lines 20-22, column 7, lines 6-22, column 8, lines 5-7). The mutant herpes simplex virus can be administered to human and non-human animals suffering from tumors and neoplasms by direct intraneoplastic inoculation (column 11, lines 45-57). Moreover, the disclosed method for killing tumors and neoplasms includes treatment of patients with malignant melanoma (column 11 lines 45-55 column 3, lines 61-67).

U.S. Patent No. 6,139,834 teaches as set forth above but does not specifically teach a method of treating a metastatic melanoma which occurs in the central nervous system/brain of a human comprising intratumoral or intracranial injection of an avirulent HSV-1 mutant 1716.

WO 92/13943 discloses HSV-I mutant 1716 and that strain 1716 contains a 759 bp deletion in each copy of the gamma 34.5 gene which is found within the BamH1 s fragment of the long repeat region of the viral genome (See page 4, lines 16-31 in WO 92/13943. The deletion is associated with non-neurovirulence (replication defect in the central nervous neuron environment) *in vivo* for strain 1716 compared to the parental wild type strain, even though strain 1716 grows as efficiently as the wild type 17+ virus (example 4, pages 20-21). Furthermore, WO 92/13943 teaches that strain 1716 has a vaccine potential because it is incapable of replicating in CNS neuron: but is able to elicit a good immunological and cell mediated response due to its ability to replicate in the peripheral tissue (page 3, lines 7-11).

Amer et al specifically teach that incidence of CNS metastases were found in 75% of patients with clinically advanced malignant melanoma wherein motor dysfunction, mental confusion, cranial nerve disturbance as well as headache were

among the most common manifestations wherein the best therapeutic results were noted after surgery for solitary CNS metastases (see abstract).

Budman et al specifically teach that CNS metastasis from malignant melanoma is a common cause of death among malignant melanoma patients (see abstract).

Bolovan et al teach that HSV-1 17+ mutants, wherein ICP34.5 gene is attenuated and the mutants are neuroavirulent, replicate efficiently *in vitro* in cells that are rapidly dividing but are avirulent in cells that are not dividing rapidly. This finding suggests that a function present in actively dividing cells was able to compensate, at least partially, for the replication restriction seen in confluent primary cultures (see p. 53, col 1) wherein the construct used is similar to the 1716 HSV-1 deletion mutant.

MacLean et al specifically teach that the avirulence of HSV-1 mutants 1714 and 1716 is due to the deletion of 759 amino acids in the ICP34.5 gene (see p. 638). The reference teaches that 1716 is a wild-type variant of 1714 wherein the identified 759 amino acids in the ICP34.5 gene have been deleted (p. 631, see abstract). Further, the 1714 mutant was shown to replicate in a wide variety of rapidly dividing cells *in vitro* including an erythroleukemia cell line, HFL and a dog kidney cell line MDCK which exhibits qualities of papillary adenocarcinoma with an efficacy similar to that of wild-type 17+ (see p. 635, Table 2).

Olafsson et al teach that HSV-1 infects metastatic melanoma cells (see p. 250).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have substituted the 1716 construct taught by WO 92/13943 for the construct of U.S. Patent No. 6,139,834 in the method of

U.S. Patent No. 6,139,834 for the treatment of melanoma because although U.S. Patent No. 6,139,834 specifically teaches that the construct of the invention is a preferred embodiment, the patent also specifically teaches that viruses have been tested in the prior art for their ability to treat various types of tumors in animals and humans via direct cell killing by the virus, called oncolysis, and that for use as antineoplastic agents these viruses have been genetically altered so that they are not capable of replication in non-dividing cells to avoid systemic infection and further because WO 92/13943 specifically teaches that the mutant virus strain 1716 is capable of killing non-neuronal tumor cells via oncolysis since it still retains the ability to replicate in the peripheral tissues. Additionally, the mutant virus strain 1716 is still sensitive to acyclovir and penciclovir because it still retains the thymidine kinase gene.

Further, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have substituted the 1716 construct taught by WO 92/13943 for the construct of U.S. Patent No. 6,139,834 in the method of U.S. Patent No. 6,139,834 for the intratumoral/intracranial treatment of CNS/brain metastatic melanoma because (A) Olafsson et al teach that HSV-1 infects metastatic melanoma cells, (B) Bolovan et al teach that a construct similar to 1716 was found to be virulent in actively dividing cells, *in vitro*, but avirulent in non-dividing confluent cells and specifically suggest that a function present in actively dividing cells was able to compensate, at least partially, for the replication restriction seen in confluent primary cultures and (C) MacLean et al specifically teach that a 17+ mutant with a deletion identical to that found in 1716 replicates in a variety of rapidly dividing cells *in vitro*, including cancer/cancer-like cell lines with an efficacy similar to that of the wild-type 17+ virus. Given the above, that is

that it was known that HSV-1 infects metastatic melanoma cells, given that it was known that constructs similar to 1716 (including the parent of 1716 with an identical deletion in the ICP34.5 gene) are virulent in rapidly dividing cells with efficacy similar to wild-type 17+ but avirulent to non-dividing cells, it would be expected that the 1716 construct would be virulent to intracranial rapidly dividing metastatic melanoma cells but not to the neural cells surrounding the metastatic tumors.

Given the above one would have been motivated to have substituted the 1716 construct taught by WO 92/13943 for the construct of U.S. Patent No. 6,139,834 in the method of U.S. Patent No. 6,139,834 for the intratumoral/intracranial treatment of CNS/brain metastatic melanoma with a reasonable expectation of success and further one would have been motivated to have substituted the 1716 construct taught by WO 92/13943 for the construct of U.S. Patent No. 6,139,834 in the method of U.S. Patent No. 6,139,834 for the intratumoral/intracranial treatment of CNS/brain metastatic melanoma because US Patent 6,139,834 specifically contemplates the treatment of melanoma with an HSV-1 mutant (which reads on intracranial metastases) and because Amer et al specifically teach that incidence of CNS metastases were found in 75% of clinically advanced patients with malignant melanoma wherein the best therapeutic results were noted after surgery for solitary CNS metastases, and further because Budman et al specifically teach that CNS metastasis from malignant melanoma is a common cause of death among malignant melanoma patients. Finally, one would have been motivated to use the 1716 construct to treat brain metastases because (A) it is neuroavirulent while virulent to rapidly dividing cells, (B) would treat CNS/brain metastatic melanoma lesions with a protocol wherein the

chemotherapeutic would kill the malignant melanoma cells but not the CNS cells which surround the metastases, (C) would allow patients to avoid the trauma induced by surgery of the brain,. Given the teachings of set forth above, one would have had a reasonable expectation of success in using the mutant HSV 1716 in killing metastatic melanoma cancer cells in CNS/brain, particularly since 1716 grows (or replicates) as efficiently as the wild type 17+ virus in rapidly dividing peripheral cells.

Applicant's arguments drawn to the rejection of claims 43-45, 47, 51, 59 in the Paper mailed October 14, 2003 are considered moot in view of the newly added references.

4. Claims 43-45, 47, 51, 59 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent No. 6,340,673 and further in view of U.S. Patent No. 6,139,834, WO 92/13943 and Amer et al, *Supra* or Budman et al, *Supra*.

The claims are drawn to a method of treating a metastatic tumor which occurs in but does not originate from the central nervous system of a human comprising intratumoral or intracranial injection of an avirulent HSV-1 consisting of an HSV-1 genome wherein such modification consists of a mutation in the gamma 34.5 gene so as to become a non-functional gamma 34.5 gene, wherein the avirulent HSV1 infects and replicates within the tumor cells of tumor, wherein the metastatic tumor occurs in brain, wherein the metastatic tumor is metastasized melanoma, wherein the modified virus is modified by deletion within the BamHI s restriction fragment of the RL terminal repeat wherein the mutant is strain 1716.

US Patent No. 6,340,673 teaches using an HSV-I virus with a specific mutation in the gamma 35.4 gene to treat cancer and tumorogenic diseases both in the CNS and in all other parts of the body in a mammal including human (see col.

5, lines 63-66, col. 9, lines 50-61 and the claims). US Patent No. 6,340,673 further teaches direct injection of the virus into the tumor or intratumorally, and that an exemplified HSV-I virus with a specific mutation in the gamma 35.4 gene is the recombinant virus R3617 or R3616 lacking 1 kb of DNA in each copy of the gamma 34.5 gene (see Table 1 of col. 17, Fig. 2). US Patent No. 6,340,673 also teach that infection of cells of neuronal origin with mutants incapable of expressing the gamma 34.5 gene resulted in shutoff of cellular protein synthesis, whereas infection of cells of non-neuronal origin with wild type or mutant viruses resulted in sustained protein synthesis and production of infectious progeny (col. 18, lines 10-15).

US Patent No. 6,340,673 teaches as set forth but does not specifically teach a method of treating a metastatic melanoma which occurs in the central nervous system/brain of a human comprising intratumoral or intracranial injection of an avirulent HSV-1 mutant, 1716.

U.S. Patent No. 6,139,834, WO 92/13943 and Amer et al or Budman et al teach as set forth above.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have substituted the disclosed construct of WO 92/13943, HSV-I mutant 1716 for the R3616 non-neurovirulent HSV-1 mutant of U.S. Patent No. 6,340,674 in the method of US Patent No. 6,340,673 because each of these agents had been taught by the prior art to be effective for the same purpose, that is the oncolysis of tumor cells and non-virulence to cells of the CNS. Further, it would have been *prima facie* obvious and one would have been motivated to make the substitution in order to treat a cancer/tumorogenic disease, that is malignant melanoma, because U.S. Patent No. 6,139,834 teaches the use of

a replication-competent viral vector, preferably a herpes simplex virus, suitable for use in humans, that is capable of killing human tumor cells *in vivo*, including melanoma, that exhibits hypersensitivity to anti-viral agents and an inability to revert to wild-type virus, and that is not neurovirulent at a dose required to kill tumor cells and the HSV-I mutant 1716 exhibits these properties.

Finally, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have substituted the 1716 construct taught by WO 92/13943 for the construct of US Patent No. 6,340,673 in the method of US Patent No. 6,340,673 for the treatment of CNS/brain metastatic melanoma because Amer et al specifically teach that incidence of CNS metastases were found in 75% of clinically advanced patients with malignant melanoma wherein motor dysfunction, mental confusion, cranial nerve disturbance as well as headache were among the most common manifestations associated with brain metastases and wherein the best therapeutic results were noted after surgery for solitary CNS metastases, while Budman et al specifically teach that CNS metastasis from malignant melanoma is a common cause of death among malignant melanoma patients in order to treat melanoma that had metastasized to the brain which as taught by Budman et al is a common cause of death from malignant melanoma. One would have been motivated to use the 1716 construct to treat brain metastases in order to avoid the trauma induced by surgery of the brain and in order to treat CNS/brain metastatic melanoma lesions with a protocol wherein the chemotherapeutic would kill the malignant melanoma cells but not the CNS cells which surround the metastases in view of the specific teaching that 1716 is avirulent toward CNS. Given the teachings of set forth above, one would have had a reasonable expectation of success in using the mutant HSV 1716 in killing

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metastatic melanoma cancer cells in CNS/brain, particularly since 1716 grows (or replicates) as efficiently as the wild type 17+ virus in peripheral cells.

Applicant's arguments drawn to the rejection of claims 43-45, 47, 51, 59 in the Paper mailed October 14, 2003 are considered moot in view of the newly added references.

5. All other objections and rejections recited in the paper mailed October 14, 2003 are hereby withdrawn.

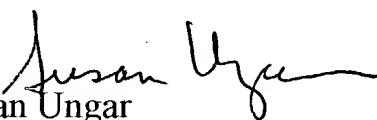
6. No claims allowed.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Ungar, PhD whose telephone number is (571) 272-0837. The examiner can normally be reached on Monday through Friday from 7:30am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvette Eyler, can be reached at 571-272-0871. The fax phone number for this Art Unit is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Effective, February 7, 1998, the Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1642.


Susan Ungar
Primary Patent Examiner
April 19, 2004